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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,838	11/29/2001	Hans Hofland	P 23,643-A USA	6395

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,838	HOFLAND ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,11,14,15,18-23 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,11,14,15,18-23 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 7, 11, 14-15, 18-32 are presently pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7, 11, 14-15, and 18-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

Instant claim 1, and those claims dependent thereon, claims 7, 11, 14-15, and 18-32, were amended to recite the following:

> A process for making a stable colloid for gene transfer, said stable colloid comprising complexes which have a neutral or net anionic surface potential and comprise sequestered DNA, said process comprising modifying a precursor colloid comprising a complex which has a cationic surface potential and comprises DNA and cationic lipids or polymers by reacting a reagent with the cationic lipids or polvmers present in said complex to reduce, remove or reverse said cationic surface potential, said reagent selected from the group consisting of citraconic anhydride and N-hydroxysuccimide acetate.

As support for the above amendment to claim 1, Applicant refer to the specification at pages 3-4 (bridging paragraph)

> In one embodiment, plasmid DNA is associated with a polyvalent cationic lipid resulting in a stable colloid with a positive surface potential. Preferred lipids contain polyvalent cationic head groups such as linear polyamines (e.g. spermine, spermidine), branched polyamines (RPR209120 cf FIG. 4) or polyamines containing guanidinium groups (RPR204014 cf FIG. 7). In addition, preferred lipids contain hydrophobic moieties that are based on one or more acyl chains of various lengths such as meristyl or palmityl. This colloid is then modified by adding an agent that reacts with the positively charged amines of the cationic lipids, thus consuming the charge of the colloid. Two preferred chemical reagents are citraconic anhydride (CCA) and NHS-Acetate.

Applicants also cite, the specification at pages 5-6, and Examples 1 and 2. However, none of these passages in the specification provide adequate support for wherein the stable colloids of the instant invention comprise multiple complexes. Throughout Applicant's arguments filed 1-26-06, constant reference is made to wherein either CCA or NHS ester is reacted with cationic lipids/polymers already present in *a DNA containing complex* to reduce, remove, or reverse the cationic charge of the complex. There is no support for wherein the stable colloid produced by this process produces multiple complexes, wherein the ***complexes*** have neutral or net anionic surface potential ***and*** comprise sequestered DNA. Claim 1 as presented in the prior amendment to the claims filed 7/13/05, recited that the stable colloid comprises *neutral or anionic complexes containing sequestered DNA*. The manner in which the claims are presently written provides the interpretation that the neutral or anionic complexes of the stable colloid may or may not contain any sequestered DNA. The presently claimed invention does not correspond to the invention as disclosed in Examples 1 or 2, which require at the start, the production of a cationic lipid particle containing DNA, wherein said particle is then reacted with either CCA or NHS ester to produce anionic or neutral particles that contain DNA.

Claim Rejections - 35 USC § 102/§ 103

5. The rejection of claims 1, 7, 11, and 14-15 under 35 USC 102(e) as being anticipated by Monahan et al. is withdrawn in response to Applicant's arguments filed 1/26/06.

6. Claims 18-23, and 30 remain rejected under 35 U.S.C. 102(e) as being anticipated by Monahan et al., or unpatentable over Monahan et al. for the reasons of record set forth in the Final Office Action mailed 3-09-05.

Applicant's arguments filed 1-26-06 have been fully considered, but they are not persuasive. According to Applicants, the process of claim 1 distinguishes over the colloid made by the Monahan et al. process, specifically Applicants state that the complex of Applicant's colloid itself has a neutral or net anionic charge, in contrast to the colloid of Monahan et al. which comprise a complex of DNA and cationic polymers which is enveloped by an additional layer of anionic polymers. Moreover, according to Applicants their colloid does not require this additional layer. Applicant's description of the claimed invention is confusing since it appears that Applicant focus on the characteristics of the "complex" of the claimed invention, and not specifically on the overall charge characteristics of the claimed "colloid." Applicant's arguments are not persuasive. Absent evidence to the contrary, since claim 18 is drawn to "a stable colloid," regardless of its method of preparation, if the prior art compound reads on a process which involves the production of a "stable colloid," the claim is unpatentable even though the prior art product was made by a different process. See MPEP § 2113 [R-1], Product-by-Process Claims: "[E]ven though product-by-process claims are limited

by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

As stated in the prior Office Action, Monahan et al. anticipates the claimed invention, since they disclose a process for the formation of a stable colloid, wherein said process comprises that the addition of citraconic anhydride to the cationic polymer poly-L-lysine, and the formation of citraconylpoly-L-lysine, and the addition of this compound to a complex of DNA and poly-L-lysine, wherein the overall zeta potential of the formed particles of this reaction is negative (see col. 25, lines 27-65). Additionally, Monahan et al. teach the use of NHS ester to react with cationic polymers to form anionic polymers. Additionally, it is clear that the invention of Monahan et al. is specifically designed for modifying DNA-polymer complexes to comprise a negative zeta potential for the express purpose of delivering nucleic acid in cells (see abstract).

7. Claims 1, 7, 11, 14-15, 18-23, and 28-30 remain rejected and amended claims 31-32 are rejected under 35 USC § 103(a) as being unpatentable over Semple (US Patent No. 6,287,591 B1) taken with Trubetskoy (US 2003/0026841 A1) and Monahan et al. (6,379,966), for the reasons of record set forth in the Final Office Action mailed 3-09-2005.

Applicant's arguments filed 1-26-06 have been fully considered but they are not persuasive. Applicant's traversal is summarized on page 11 of Applicant's response filed 1-26-06:

> Traversal of the Examiner's
> Section 103 Rejection Based on Semple et al., Monahan et al., and Trubetskoy et al.
>
> The Examiner has rejected independent Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 as being rendered obvious under Section 103(a) by:
>
> (A) U.S. Patent No. 6,287,591 to Semple et al., which discloses the use of a buffer to change the surface potential of a DNA-cationic lipid complex to render it neutral; in view of
>
> (B) Monahan et al., which discloses the use of CCA to react with a cationic polymer to render it anionic and the use of the resulting anionic polymer in the formation of an anionic layer around a DNA-cationic polymer complex; and
>
> (C) U.S. Application Publication No. 2003/0026841 to Trubetskoy et al., which claims priority to a provisional application filed on December 31, 1999 and discloses the use of anionic compounds in the formation of an anionic layer around a DNA-cationic polymer complex and states further that the addition of certain anionic compounds may destabilize the complex.
>
> Neither Monahan et al. nor Trubetskoy et al. teaches the reaction of a reagent with the cationic lipids/polymers already present in a DNA-cationic lipid/polymer complex.

8. Applicants summarized the rejection of the instant claims over the combined teachings of Semple et al., Trubetskoy et al. and Monahan et al., by stating that "[N]either Monahan et al. nor Trubetskoy et al. teaches the reaction of a reagent with cationic lipids/polymers already present in a DNA-cationic lipid/polymer complex. There is no consideration here of how the combined references read on the claimed invention. In response to applicant's arguments against the references individually, one cannot

show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Contrary to Applicant's assertions, the invention of Monahan et al. is drawn to methods for modifying DNA-polymer complexes to comprise a negative zeta potential for the express purpose of delivering nucleic acid in cells (see abstract). In specific a embodiment, Monahan et al. teach that the addition of citraconic anhydride to the cationic polymer poly-L-lysine, and the formation of citraconylpoly-L-lysine, and the addition of this compound to a complex of DNA and poly-L-lysine, wherein the overall zeta potential of the formed particles of this reaction is negative (see col. 25, lines 27-65). Moreover, as stated by Applicants above, Monahan et al. teach the use of NHS ester to react with cationic polymers to form anionic polymers. Although, Monahan et al. does not teach directly modifying the poly-L-Lysine-DNA complex directly with either citraconic anhydride or N-hydroxysuccinimide acetate, it is noted that Applicant's claims are not limited to such a process. The instant claim 1 (lines 6-8) has been amended to recite, "reacting a reagent with the cationic lipids *or* polymers present in said *complex.*" There is no requirement that "said complex" comprises sequestered DNA as suggested by Applicant's arguments.

Again, contrary to Applicant's assertions, one of ordinary skill n the art would have been motivated to modify the DNA-lipid compounds of Semple et al. with a compound that would reduce, remove or reverse the positive charges on the surface of

the disclosed DNA-lipid compounds since Semple et al. (see col. 9) teach the following (as set forth in the Office Action mailed 9/09/04, see page 8):

> The methods and composition of the invention make use of certain lipids which can be present in both a charged and an uncharged form. For example, amino lipids which are charged at a pH below the pK_a of the amino group and substantially neutral at a pH above the pk_a can be used in a two-step process. First, lipid vesicles can be formed at the lower pH with (cationic) amino lipids and other vesicle components in the presence of nucleic acids. In this manner the vesicles will encapsulate and entrap the nucleic acids. Second, the surface charge of the newly formed vesicles can be neutralized by increasing the pH of the medium to a level above the pK_a of the amino lipids present, i.e., to physiological pH or higher. Particularly advantageous aspects of this process include both the facile removal of any surface adsorbed nucleic acid and a resultant nucleic acid delivery vehicle which has a neutral surface. Liposomes or lipid particles having a neutral surface are expected to avoid rapid clearance from circulation and to avoid certain toxicities which are associated with cationic liposome preparations.

The teachings of Semple et al. clearly suggests modifying the surface of DNA/cationic lipid particles containing formulation, the particles would resist degradation from *in vivo* circulation and not produce certain toxicities, which are associated with cationic liposome preparations. Along this same rationale, Trubetskoy et al. (see page 5, paragraph 52) Monahan et al. (col. 23) provide motivation for a recharging process as applied to reducing the cationic charge on liposomal vessels, to thereby enhance the efficiency of gene transfer *in vivo*. Moreover, the very reagents that Applicants use for "recharging" the cationic charge on the recited cationic lipids or polymers present in said complex are disclosed in Monahan et al. (CCA and NHS ester), for use in the same purpose, namely for the treatment of cationic polymers to confer a negative charge in the design of a stable DNA-lipid complex for delivery into a cell. Furthermore, Trubetskoy et al. teaches that an addition of polyanionic molecules to a lipid/DNA complex would enhance the transfer activity of a DNA/cationic lipid complex.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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